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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/427,657	ALITALO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-18 and 21-100* is/are pending in the application.

4a) Of the above claim(s) *21,33-48 and 59-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-18, 22-32, 49-58, 63-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 05/07/04 and 03/04/04 has been acknowledged.

Claims 9, 19-21, 30, 33-48 and 59-62 directed to the non-elected invention are canceled.

Claims 1-8, 10-18, 22-29, 31-32, 49-58, 63-100 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121). The fax phone numbers for the organization where this application or proceeding is assigned is ***703-872-9306****.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-8,10-18, 22-29, 31-32, 49-58, 63-100 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a mammalian subject to inhibit restenosis of a blood vessel by administering to the subject at the site of restenosis a replication-defective adenovirus vector comprising a polynucleotides sequences encoding VEFG-C polypeptide (SEQ ID NO:2), does not reasonably provide enablement for a method of treating restenosis by administering a nucleic acid sequence which encodes any portion or variant of amino acid sequences of SEQ ID NO:2 (as claimed), wherein the nucleic acid is administered using any viral or non viral vector. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

The invention relates to a method of gene therapy for restenosis.

Breadth Of Claims and Guidance Provided in the Specification:

The scope of invention as claimed encompasses the treatment of restenosis by administering any viral or non-viral vector comprising a polynucleotide sequence, which encodes the VEFG-C polypeptide. The scope of invention as claimed further encompasses the use of any VEGF-C sequence and any unknown allelic form of VEGF-C. The scope of VEGF-C analogs or variants encompasses fragments of VEGF-C polypeptide encoded by amino acid sequences 1-21, 30-131 and 211-419 of SEQ ID NO:2, lacking 32-102 or 228-419 of SEQ ID NO:2, any fragment of that binds to VEGFR-2 or VEGFR-3 and any polynucleotide that hybridizes to VEGF-C cDNA (SEQ ID NO:1), wherein the fragment as claimed is capable of binding to VEGFR-2 and VEGFR-3 receptors and inhibits restonosis in a blood vessel. In addition the scope of invention as claimed encompasses a kit or formulation to treat restenosis comprising a nucleic acid sequences that promotes the expression of VEGF-C in cells of a blood vessel.

At best the specification teaches the use of adenovirus-mediated VEGF-C gene transfer in rabbit restenosis model The specification teaches an adenovirus vector containing the cDNA encoding the complete human prepro-VEGF-C open reading frame operably linked to CMV promoter and human growth hormone polyadenylation signal sequence. The specification further teaches balloon denudation of rabbit aorta followed by adenovirus mediated gene transfer after 3 days. The specification concluded that VEGF-c gene transfer significantly reduced intimal thickening at two weeks time point after aortic denudation and after vessel wall damage caused by the gene transfer catheter with out balloon denudation (Spec. pages 25-28 example-1).

However the specification fails to disclose that the gene transfer of a portions of SEQ ID NO:2 which comprises amino acid 30-131 and 211-419 of SEQ ID NO:2; a polypeptide sequence which lack amino acids 228-419 of SEQ ID NO:2; a polypeptide

sequence which lacks amino acid 32-102 of SEQ ID NO:2 inhibits restenosis in a mammalian subject. Furthermore the specification fails to disclose that any unknown of allelic form of VEGF-C (nucleotide sequence which hybridizes the nucleic acid encoding the amino acid sequence of SEQ ID NO:2) would inhibit the restenosis of blood vessel in a mammalian subject. At best the specification only teaches an adenoviral-mediated-VEGF-C gene transfer. The specification fails to disclose that the administration of any other viral or non-viral vector would successfully deliver the VEGF-C gene to the cells of a blood vessel for the inhibition of restenosis.

State Of Art And Predictability:

Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. For example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to

transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4).

In instant case besides an adenoviral vector the specification fails to disclose the use any other viral or non-viral vector that resulted in expression of VEGF-C in blood vessels to treat restenosis. Furthermore the pathophysiology of restenosis is incompletely understood and the technical barriers to achieving robust intra coronary gene transfer have not been overcome. For example it is unpredictable that a retroviral vectors would be able transfect non dividing blood vessels cells in the treatment of restenosis, since the retroviral vectors only infects actively dividing cells. (DeYong et al Circ Res 82;306-313, 1998 page 309, col.1).

Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3).

VEGF-C binds to VEGFR-2 and VEGFR-3 and has been show to stimulate both angiogenesis and formation of lymphatic blood vessels (Hiltunen et al Circulation 102:2262-2268, 2000). In instant case the specification fails disclose that gene transfer of a portion of SEQ ID NO:2 (as claimed) would inhibits restenosis of a blood vessel. It is well known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The segments or variants of VEGF-C as claimed are mere hypothetical polypeptide because no biological function has been established. The mere identification of critical regions would not be

sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. Therefore, Applicant has not presented enablement commensurate in scope with the claims which encompasses a portion or variant of SEQ ID NO:2. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976).

Response to arguments

The applicant argues that the recent amendment provides additional structural and functional definition for the encoded VEGF-C polypeptide i.e. full length prepro-VEGF-C (SEQ ID NO:2), active fragments thereof and a genus of analogs wherein the amino acid sequences has been deleted, added or replaced (response page 19, response 05/07/04). The applicant argues that the specification explains that various fragments as claimed are able to bind to VEGF-3 or VEGFR-2 and it is expected that the polypeptide fragments as claimed will retain VEGF-C biological activity. The applicant further argues that various patents has been issued, including claims that embrace number of biologically active VEGF-C forms other than the exact sequence used in the working example of this application. The applicant argues that the fragments as claimed are not hypothetical polypeptides, since the functional activity of the fragments as claimed can be evaluated by VEGF-C activity assay as disclosed in WO98/33917. The applicant argues that the office action fails to establish that the treating a mammalian subject by administering any viral of non-viral vector encoding any fragment of VEGF-C is unpredictable. The applicant argues that medical research by definition has involved and continues to involve with considerable experimentation and gene therapy is not unique in this respect, and it does not imply "undue experimentation," in evaluating the present claims for enablement. Discussing the specific references cited by the office (regarding treating restenosis) the applicant argues that had DeYoung and Dichek Known about the applicants research they very well may have come to a more positive assessment regarding the use of gene therapy

to treat restenosis. In addition the applicant cited various post filing research articles to conclude that invention as claimed is fully enabled.

However, applicant's arguments are found NOT persuasive because the applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). Each patent application is examined on its own merit and is considered enabled in view of its own disclosure. The issue is not whether the other application support their claims but whether one supports its claims "[i]t is immaterial whether similar claims have been allowed to other" In re Gialito 188USPQ 645,648 (CCPA 1976). At best the specification teaches the use of adenovirus-mediated VEGF-C gene transfer in rabbit restenosis model. Besides the nucleic acid which encodes the amino acid sequence of SEQ ID NO:2, the specification as failed fails to disclose any other variant or fragment of SEQ ID NO:2 (as claimed) is capable of inhibiting the restenosis of blood vessel in any mammalian subject.

The office has provided clear evidence that the pathophysiology of restenosis is incompletely understood and the technical barriers to achieving robust intra coronary gene transfer have not been overcome. The current utility of gene transfer vectors achieve robust intracoronary gene delivery have not been overcome, since the current utility of gene transfer vectors for effective human coronary delivery is low and the potential for harmful side effects of coronary gene delivery is high (page 306, col.2 para.2). In addition arterial lesions in balloon-injured arteries of experimental animals are highly cellular and achievement of robust levels of recombinant gene expression my account for success of antiproliferative gene therapy. In contrast advanced human coronary lesions are often acellular with necrotic cores, dense fibrous tissue and calcification. Therefore high levels of recombinant gene expression will not be achieved by infusing any gene transfer vector in such largely non-dividing tissues (page 307, col.2 para. 3). For example it is unpredictable that a retroviral vectors would be able transfect non dividing blood vessels cells in the treatment of restenosis, since the retroviral vectors only infects actively dividing cells (page 309, col.1) Furthermore, despite limitation that VEGF might prevent initial thickening VEGF gene delivery does not currently appear initial for application to human coronary restenosis. Two

independent studies suggest that VEGF delivery may actually worsen arterial hyperplasia (DeYong et al Circ Res 82;306-313, 1998, page 309, col.1 para.3).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Thus considering the limited amount of guidance provided in the specification and unpredictability in the state of the art, the gene based therapies to treat restenosis using any variant of VEGF-C in any viral or non-viral vectors is not considered routine and without sufficient guidance to a specific expression vector ending the specific gene fragment which is capable of treating restenosis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include making any viral or non viral vector encoding any segments or variant of SEQ ID NO:2 (as claimed) and evaluation of inhibition of restenosis by each segment and/or variant of SEQ ID NO:2.

Claim Rejections - 35 USC § 102

Claims 29, 71-72, 98 and 100 stand rejected under 35 U.S.C. 102(b) as being anticipated by Alitalo (W/O 97/05250, ref of record) for the same reasons of record as set forth in the office action mailed on 10/02/03.

The instant claims are directed a kit or a formulation, which essentially are nucleotide sequences or vectors encoding the polypeptide VEGF-C.

Alitalo teaches nucleotide sequences which matches 100% to the nucleotide sequence of SEQ ID NO: 1 which encodes the amino acid sequence of SEQ ID NO:2 (VEGF-C). The cited art further teaches human VEGF-C cDNA inserted in an expression vector (page 49 example-11). The cited art further teaches that VEGF-C polypeptide stimulates the tyrosine phosphorylation fo VEGFR-3 and VEGFR-2 receptors (page 57 lines 30-35). Therefore the cited art clearly anticipate the invention as claimed.

Response to arguments

The applicant amended claims 29, 71-72, 98 and 100 to delete claim limitation that requires the presence of "a label attached to or packaged with the container". However, the applicant fails to file any response that after the recent amendment filed on 05/07/04 the invention as claimed is not anticipated by Alitalo who clearly teaches a nucleotide sequences which matches 100% to the nucleotide sequence of SEQ ID NO: 1 which encodes the amino acid sequence of SEQ ID NO:2 (VEGF-C). Thus claims 29, 71-72, 98 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Alitalo (W/O 97/05250, ref of record) for the same reasons of record as set forth in the office action mailed on 10/02/03.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to ***(571) 272-0547.***

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306.**

Sumesh Kaushal
Examiner GAU 1636

JEFFREY FREDMAN
PRIMARY EXAMINER